apply equally to either family of filings. In these circumstances, Richard Schwartz (BPS) in the interview indicated a rejection would be permissible only after a heightened standard of review requiring approval by the group director. It is acknowledged that the present office action has been signed by the group director. However, because the Examiner does not agree that the present claims are patentably indistinguishable from those in the Florida patents or that her comments cast doubt on the Florida patents, the record is unclear as to what the group director has approved.

11. The Examiner says that she has indicated that the present claims and those of the '937 patent are not co-extensive in scope. However, the Examiner has not said why she believes there is a difference in scope. If the Examiner is correct that the present claims are patentably distinct from the claims in the '937 patent (and the '360 patent), then applicants can overcome these patent by supplying evidence of derivation by declaration rather than interference. Therefore, Applicants request that the Examiner indicate which, if any, of the present claims are deemed patentably distinct from those in the '937 and '360 patents and why.

13-18. The Examiner essentially repeats comments from previous office actions regarding alleged lack of enablement of the claimed methods. In response, Applicants now provide a report indicating that a phase I human clinical trial for the use of GAD in treating or preventing type I diabetes has been successfully conducted, and that a phase II trial has been approved, and will shortly be conducted. The report also indicates the previous articles in the scientific literature that administration of GAD to diabetes-prone animals provided a basis for the clinical trials. The fact that the phase I trial was successful is itself evidence that side-effects that administration of GAD to humans does not cause side effects. Moreover, the fact that clinical trials are in progress indicates that those in the field believe that the prior preclinical work in the field, including the tests in rodent models that have been discussed in previous prosecution, are sufficiently predictive of success in humans to justify the large costs and potential risks inherent in conducting human clinical trials.

The Examiner's comments are now addressed in turn. First, the Examiner says that treatment may be effective only in prophylaxis of treatment which is not possible due to

the unpredictability of the onset of IDDM. However, the Examiner appears to overlook the fact that the application discloses that onset of IDDM can be predicted from the presence of autoantibodies to GAD in the serum. Such autoantibodies are present several years before onset of disease.

Second, the Examiner criticizes the application for not disclosing dosages or route of administration. However, the Examiner has overlooked the guidance that has been provided as to both dosage and route of administration at pp. 20-21 of the specification. Specifically, the application identifies a typical range of dosages of about 1 to 500 mg GAD per kg body weight with a preferred range of about 5 to 25 mg/kg body weight. The application also refers to parental administration and, in particular, to intravenous administration. It is noted that dosage of the order of 100 micrograms to 2 mg per mouse have proved successful in tolerization of mice (see Elliot, *Diabetes* 43, 1494-1499 (1994) and Petersen, *Diabetes* 44, 1478-1484 (1994)). Taking into account the different mass of mice and humans, these dosages are certainly within the order of magnitude contemplated by applicants. Further, Harrison, *Molecular Medicine* 1, 722-727 (1995) (of record) at p. 724, column 1 reports that at least three parenteral routes of administration, including intravenous administration of GAD delay the onset or reduce the incidence of IDDM. Accordingly, the application does teach dosages and routes of administration that are sufficient to obtain pharmacological activity in experimental animals.

Next, the Examiner repeats previous comments regarding possible difficulties resulting from the existence of multiple autoantigens in diseases such as IDDM. However, the Examiner does not address applicants' response to this point (paragraph bridging pp. 5-6 of response of October 28, 1998). To recap, it has been reported that a T-cell response to GAD65 develops early in development of IDDM and subsequently spreads to other β-cell antigens in a cascade of responses that ultimately lead to IDDM (see Tian et al., *Nature Medicine* 12, 1348 (1996), column 1, first paragraph). Thus, it would be expected that inducing tolerance to GAD65 would abort subsequent events in the cascade of events leading to IDDM. This expectation is supported by the several publications reporting that GAD65 or peptides thereof inhibit development of IDDM in laboratory animals (see e.g., Tisch et al. (BO), Kaufman (BG), Tian et al., *supra*, Peterson et al., *Diabetes* 44, 1478 (1994), and Pleau et al., *J. Immunol.*

Immunopath. 76, 90-95 (1995)). Moreover, it is evident that those in the field conducting clinical trials and the regulatory authorities that have approved them do not believe that the existence of multiple antigens will be detrimental.

Next, the Examiner reiterates a specific phrase in the Lernmark reference stating that other investigators have not found published procedures to be easily reproducible (office action at paragraph (11)). Applicants response is that the Examiner is giving undue emphasis to a brief and passing comment at the expense of the totality of numerous publications in peer-reviewed journals already of record indicating that GAD shows a pharmacological activity in treatment of IDDM in animal models. The only reference cited by Lernmark in the excerpt referred to by the Examiner is Petersen, *Diabetes* 44, 1478-1484 (1994) (of record). However, this reference provides evidence that GAD can be successfully used to delay the onset of diabetes in neonatal NOD mice, and thus supports rather than contradicts enablement of the present claims.

Next the Examiner cites Harrison (1995) as indicating that for the present insulin is the only antigen justifying therapeutic intervention to humans. This comment has clearly been superseded by the fact that clinical trials have been conducted and are in progress based on treatment with GAD.

Next the Examiner refers to Petersen (1997), a reference discussing administration of GAD to the BB rat, apparently as evidencing that extrapolation of results from mice to human may be misleading. In the previous response, Applicants explained why the BB rat was a less useful model for treatment of IDDM in humans than the NOD mouse in which pharmaceutical activity had been detected (response of April 14, 2000 at p. 5). The Examiner does not address this explanation. Moreover, if in 1997 Petersen might have been construed in the manner proposed by the Examiner, it is apparent that this construction has been superseded. The attached reports on human clinical trials indicates that those in the field do think that pharmacological activity in mice is sufficiently predictive of success in humans to justify conducting human clinical trials.

Finally, the Examiner cites an earlier Petersen reference (1994) as teaching that GAD autoimmunity is necessary, but not sufficient for development of NOD mouse diabetes, presumably implying that administration of GAD is not sufficient to prevent or treat IDDM in

humans. Applicants disagree with this position for reasons indicated above (discussion of multiple antigens). Nevertheless, it is apparent that whatever validity this view may have had in 1994 has been superseded by later events. The fact that clinical trials are now in progress indicates that those in the field and the regulatory authorities that approve them believe that prospect of success sufficient to justify the costs and potential risks of such trials.

In summary, the numerous experiments that have been published for administration of GAD to experimental animals demonstrate a pharmacological activity that is regarded by those in the field as being predictive of therapeutic activity in humans. The procedure used is a simple one involving administration of a single protein to the animal. Such has been achieved using dosages of the same order as disclosed in the specification and using several routes of administration including routes disclosed by the specification. It is respectfully submitted that the law of enablement requires no more.

19-23. Claim 31 stands rejected as anticipated by Atkinson, US 5,762,937. Applicants reiterate that this issue should be determined by interference. Nevertheless, if the Examiner is of the view that any of the presently pending claims are patentably distinct over Atkinson, Applicants will provide declarations to overcome the cited reference on the basis of derivation.

It is noted that the office action does not indicate the disposition of claims depending from claim 31.

26-28. Claim 35 and 54-57 stand rejected as obvious over Chang & Gottlieb The Examiner acknowledges that Chang & Gottlieb do not teach a composition comprising GAD in a pharmaceutically acceptable carrier for human use. However, the Examiner says that it would have been obvious to modify Chang & Gottlieb's composition in view of the fact that Chang & Gottlieb teach a carrier suitable for use in rats, and that carriers suitable for use in humans were known. This rejection is respectfully traversed.

Although it is agreed that pharmaceutically acceptable carriers for human use were known, mere knowledge of existence does not provide motivation for one to use such a carrier in place of the Freund's adjuvant used by Chang & Gottlieb. There are an infinite number of known substances that were available, and could have been combined with GAD.

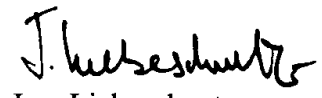
The issue is why one would have chosen a pharmaceutical carrier for use in humans rather than the Freund's adjuvant that Chang & Gottlieb actually used. The only reason that one would have been motivated to use such a carrier is if one intended to use GAD for administration to humans. However, the rationale for administering GAD to humans is disclosed by the present application and not by the prior art, namely, that GAD has a therapeutic activity. In the absence of motivation, the issue of "reasonable expectation of success" does not arise.

29. The Examiner requests support for new claims 60-61. These are supported by original claim 31 and the original disclosure. Claim 60 differs from claim 31 in that claim 60 recites "preventing or delaying" rather than "inhibiting." "Inhibiting" and "delaying" are used synonymously in the two claims. Insofar as "preventing" means something different, then additional support is provided by the present specification at p. 7, line 19. Claim 60 also differs from claim 31 in referring to "clinical symptoms" of IDDM rather than IDDM. However, IDDM is a disease that inherently has clinical symptoms. Therefore, prevention of IDDM, as disclosed by the present specification, inherently includes prevention of clinical symptoms of IDDM. Claim 60 also differs from 31 in referring to an "animal" rather than a "patient." However, in the absence of indication to the contrary an animal can be a patient and vice versa. This is merely a difference in semantics. Finally, claim 60 differs from claim 31 in reciting that the GAD is "essentially pure." However, the present specification discloses that homogeneous peptides of at least 99% w/w can be obtained (p. 14, lines 12-14). Again, it is submitted that the difference in terminology is merely semantic. Claim 61 is supported by e.g., p. 12, lines 25-29.

The written description requirement does not require *in haec verba* antecedence in the originally filed application. *Staehelin v. Secher,* 24 USPQ2d 1111, 1117 (Fed. Cir. 1991). All that is required is that the description convey with reasonable clarity to person of skill in the art that the inventor was in possession of whatever is now claimed. *Vas-Cath v. Mahurka,* 19 USPQ2d 1111,1117 (Fed. Cir. 1991). Here, such differences in wording that exist between the copied claims and the present disclosure are merely semantic or inherent in the present disclosure. The original specification and claims evidence that the present inventors were in possession of what is claimed in the Florida patent.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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Amendment

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Attorney Docket No. 2307AA-031220US
Client Ref No. 90-160-5

OIPE JC104 JAN 10 2001 PATENT & TRADEMARK OFFICE

In re application of: Steinunn Baekkeskov et al.

Application No.: 08/838,486

Filed: April 7, 1997

Group Art Unit: 1644

For: IMPROVED METHODS FOR THE DIAGNOSISD AND TREATMENT OF DIABETES

Date: January 05, 2001

I hereby certify that this is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231

Signed: J. Liebeschuetz

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THE ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

[X] Enclosed is a petition to extend time to respond.
[ ] Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.
[ ] A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.
[X] Report titled "Diabetes vaccine completes phase-I clinical trials"

If any extension of time is needed, then this response should be considered a petition therefor.
The filing fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA
TOTAL	* 18	MINUS	** 20	= 0
INDEP.	* 4	MINUS	*** 3	= 1
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDIT. FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDIT. FEE
x $9.00 =			x $18.00 =	$0.00
x $40.00 =	40.00		x $80.00 =	
+ $135.00 =			+ $270.00 =	
TOTAL ADDIT. FEE	40.00	OR	TOTAL	

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, then write "3" in this space. The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.

[ ] No fee is due.

Please charge Deposit Account No. 20-1430 as follows:

[X] Claims fee $ $40.00
[X] Any additional fees associated with this paper or during the pendency of this application.

2 extra copies of this sheet are enclosed.

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